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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: PHARMACEUTICAL COMPOSITIONS FOR THE NASAL ADMINISTRATION OF ANTIVIRAL AGENTS

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

❷ Applicant's details

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Agent's name ERIC POTTER CLARKSON

Agent's address ST MARY'S COURT
ST MARY'S GATE
NOTTINGHAM

Postcode NG1 1LE

Agent's ADP number 1305010

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⑤ Claiming an earlier applicati n date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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Please supply duplicates of claim(s), abstract, description and drawing(s).

Ch cklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)	1	Description	9
Abstract	0	Drawing(s)	0

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Pharmaceutical Compositions for the Nasal Administration of Antiviral Agents

The present invention relates to compositions for nasal administration and, more particularly, to compositions for nasal administration of antiviral agents.

Prior Art

Viral infections affecting the nasal cavity such as influenza and rhinoviral infections can be not only unpleasant disease conditions in normal individuals, but in certain 'at risk' groups represent a serious threat to health.

A variety of agents are now available that can be considered as a possible mode of treatment. These include low molecular weight antiviral agents such as Enviroxine, Pirodavir (Patent EPO398427A1 and other agents as described in EPO398425A1, EPO320032A1, EPO156433B1, EPO398426A1 and EPO435381A1) as well as antiviral proteins such as interferon-alpha and sialidase inhibitors (see for example Von Itzstein et al. Nature. 363 418, 1993). More recently it has been shown that rhinoviruses attach to tissue sites via a specific adhesion process and consequently the binding of virus can be prevented using a cell adhesion molecule such as ICAM-1 or its fragments. (Martin et al., A soluble form of intercellular adhesion molecule-1 inhibits rhinovirus infection, Nature 344, 1990, 70-72).

While such antiviral materials can be shown to be effective in vitro using appropriate tests on virus inhibition or binding blockage, it is found that such systems are not effective in vivo for example using the nasal route of administration or have to be given in high and frequent doses that can give rise to toxic effects (Hayden et al. New Eng. J. Med. 314, 71 (1986)) or could be disadvantageous on cost grounds. (Al-Nakib, W.et al. Antimicrobial Agents and Chemotherapy 33, 522 (1989)).

Therefore, it would be a significant advantage if it was found possible to increase the effectiveness of antiviral compounds in the nasal cavity. We have discovered that this can be achieved using bioadhesive gelling systems such as drug loaded microspheres, the bioadhesive cationic polymer chitosan or the in situ gelling materials such as gellan gum. These systems not only slow the process of mucociliary clearance but also provide a controlled release effect. The nasal administration of starch microspheres has been described by Illum in various patents or patent applications. In US4847091 she described how the low molecular weight drug, sodium cromoglycate, could be complexed to the surface of DEAE-dextran microspheres in order to increase residence time in the nose and to provide prolonged

local treatment in the nasal cavity. PCT/GB88/00836, PCT/GB90/101676 describe how microspheres can be used to increase the systemic uptake of poorly transported molecules such as peptides and proteins. A preferred material was starch. The use of such microspheres for the local treatment of rhinoviral infections was not described nor was their use for the controlled delivery of antiviral drugs mentioned.

The use of Chitosan as a bioadhesive material to improve the absorption of polar drugs from the nasal cavity and across other mucosal surfaces has been described by Illum in Topics in Pharmaceutical Science 1991. Editors: Crommellin D.J.A and Midha, K.K., Stuttgart, Medpharm., 1992, p 71 and in PCT GB9000291. The use of Chitosan systems for the delivery of antiviral agents for local treatment was not described. Chitosan systems for local application have been described by Partain (US 4946870). He described systems that formed substantive films in contact with topical surfaces. The various examples provided by Partain are intended for application as lotions to the skin. Intranasal administration is mentioned in US 4946870 but no examples of systems that are film forming in the nasal cavity are declared. It is also noted that in order to form coherent and substantive films the Partain examples contain high quantities of volatile material such as ethanol. This method would be precluded in the nasal application of such systems.

The use of gellan gum as an in-situ gelling material has been described in AUS 86.63189, with reference to ophthalmic applications. The possible use of gellan as a galenic form intended for contacting with mucous membranes was disclosed but no examples were given. No reference was made to a possible use of this material for the controlled release of antiviral compounds intended for nasal delivery. The drugs which could be administered by means of the ophthalmic composition according to the invention included antiviral agents such as acyclovir, adenosine, arabinoside, interferon and interferon inducing agents. The pharmaceutical uses of gellan gums and their rheological properties have been described by Deasy et al. Int. J. Pharm. 73 117 (1991) and Kublik and Muller, Eu. J. Pharm. Biopharm 39 192 (1993) and Sanzgiri et al. J. Control. Rel. 26 195 (1993).

We describe herein novel nasal delivery systems for antiviral agents based upon the principle of bioadhesion and slow release.

The bioadhesive formulations delay the clearance of the antiviral from the nasal cavity and thereby give an improved clinical effect. Fewer doses of the agent are required since the drug has a longer period of residence in the nasal cavity. The formulations described herein are particularly suitable for the delivery of macromolecular antiviral agents such as α-interferon, ICAM-1 and sialidase inhibitors as well as for low molecular rhinoviral agents such as pirovadir. We have discovered that a Chitosan spray applied nasally is useful in this

regard. The spray uses a low concentration of Chitosan. The spray when applied nasally does not produce a substantive film. A concentration of Chitosan in the range 0.2 - 2.0% is suitable. The Chitosan formulation can be administered using a conventional nasal spray familiar to those skilled in the art.

The microsphere systems can be prepared from a suitable material such as starch, gelatin, albumin, alginate, gellan, hyaluronic acid and Chitosan. These microspheres can be prepared by emulsification procedures or by spray drying. Both are established procedures in pharmaceutical formulation and are familiar to those skilled in the art. Such microspheres can be cross-linked to provide a suitable structure. The microspheres can be of a size from 1 to 200 micron. The preferred size is 10-100 microns.

The drug-microsphere formulations are prepared as a freeze-dried or spray dried powder system or a physical mixture. The microspheres can be administered by a nasal insufflator or a device that would be normally used for deposition of powders into the lungs but suitably modified for nasal administration. Examples include the Ventolin inhaler (from Glaxo) and the Dura Dry Powder Device (US Patent 5327883).

The bioadhesive microspheres have the property of swelling in water. This swelling nature leads to a preferential binding to the mucosal surface of the nose thereby leading to improved retention. The degree of swelling should be such that the particle increases its diameter (as measured by a suitable technique such as the light microscope, laser diffractomer) when immersed in water by a factor of at least 1.2 times. The preferable increase in diameter is 1.5 times or greater. The formulation can either be prepared by freeze drying from a suspension of the microspheres in drug solution or by mechanically mixing the freeze dried, spray dried or dried microspheres with the drug in a powder form. Alternatively the drug can also be incorporated into the microspheres during production. The technique of spray drying or an emulsification technique or other techniques known to the person skilled in the art can be used to produce microspheres of the desired size that contain the drug. The conditions of preparation are selected by the person skilled in the art to provide particles that have the necessary integrity and also to maintain the biological activity of the drug. This is of special importance when a spray drying process is used together with a cross-linking agent such as glutaraldehyde since this agent can also cross-link and inactivate drugs, particularly polypeptides. With Chitosan the conditions are chosen so that the microspheres retain a positive charge. This is important since Chitosan interacts with negatively charged sialic acid residue in mucins and thereby provides an electrostatic mechanism for bioadhesion.

The microspheres can be hardened by well known cross-linking procedures such as heat treatment or by chemical cross-linking agents. Suitable agents include dialdehydes,

including glyoxal, malondialdehyde, succinicaldehyde, adipaldehyde, glutaraldehyde and phthalaldehyde, diketones such as butadione, epichlorohydrin, polyphosphate and borate. Dialdehydes are used to cross-link proteins such as albumin by interaction with amino groups and diketones form schiff bases with amino groups. Epichlorohydrin activates compounds with nucleophiles such as amino or hydroxyl to an epoxide derivative.

The composition of the invention may also be a liquid formulation comprising a polymer material. The polymeric material should provide a viscous solution to aid retention in the nasal cavity. Preferably the material will gel when in contact with the nasal mucosa.

Suitable polymeric materials include gellan gum, welan, rhamsan, alginate, carboxymethylcellulose, sodium alginate, xanthan, agar, guar derivatives such as carboxymethyl guar gum, carageenan, keratan, dermatan, pectin. Polysaccharides and derivatives are particularly suitable ("Polysaccharides and derivatives" edited by R.C. Whistler and J. N. BeMiller (3rd Ed.) Academic Press, San Diego 1993).

A preferred material is gellan gum which is the deacetylated form of the extracellular polysaccharide from Pseudomonas elodea. Native/high-acylgellan is composed of a linear sequence of tetra-saccharide repeating units containing D-glucuronopyranosyl, D-glucopyranosyl and L-rhamnopyranosyl units and acyl groups.

Another preferred material is alginate. Alginate is composed of two building blocks of monomeric units namely β-D-mannuronopyranosyl and α-guluronopyranosyl units. The ratio of D-mannuronic acid and L-guluronic acid components and their sequence predetermines the properties observed for alginates extracted from different seaweed sources.

Welan is produced by an Alcaligenes species. Welan has the same basic repeating unit as gellan but with a single glycosyl sidechain substituent. The side unit can be either as α-L-rhamnopyranosyl or an α-L-mannopyranosyl unit linked (1->3) to the 4-0 substituted β-D-glucopyranosyl unit in the backbone.

Rhamsan is produced by an Alcaligenes species. Rhamsan has the same repeating backbone unit as that of gellan but with a disaccharide side chain on 0-6 of the 3-0-substituted β-D-glucopyranosyl unit. The side chain is a β-D-glucopyranosyl-(1-6)- α-D-glucopyranosyl unit.

Xanthan is produced by a number of Xanthomonas strains. The polymer backbone, made

up of (1-4)-linked β-D-glucopyranosyl units is identical to that of cellulose. To alternate D-glucosyl units at the 0-3 position, a trisaccharide side chain containing a D-glucoronosyl unit between two D-mannosyl units is attached. The terminal β-D-mannopyranosyl unit is glycosidically linked to the 0-4 position of the β-D-glucopyranosyluronic acid unit, which in turn is glycosidically linked to the 0-2 position of an α D-mannopyranosyl unit.

Carrageenan is a group of linear galactan polysaccharides extracted from red seaweeds of the Gigartinaceae, Hypneaceae, Solieriaceae, Phyllophoraceae and Furcellariaceae families that have an oster sulfate content of 15-40% and contain alternatively (1->3)-α-D- and (1->4)-α-D- glycosidic linkages.

Agar is a hydrophilic colloid extracted from certain marine algae of the class Rhodophyceae where it occurs as a structural carbohydrate in the cell walls (see also Kang and Pettitt: Xanthan, Gellan, Welan and Rhamsan in Industrial gums by Whistler and BeMiller (Eds), Academic Press Inc. London, 1993).

Mixtures of gellan with other polymers such as alginate can be used, gelling of the mixture being caused by the gellan gum. Other combinations of gums can also be used, particularly where the combination gives a synergistic effect, for example in terms of gelation properties. An example is xanthan - locust bean gum combinations.

The advantage of gellan over other materials is that it can be administered as a fluid system but in the nasal cavity the system will gel, thereby providing a bioadhesive effect and holding the drug at the absorptive surface for an extended period of time.

The grade of gellan gum can be Gelrite or Kelcogel from Kelco Int. Ltd. or other similar grades from other manufacturers. The gellan can be prepared at a concentration of 0.1 w/v to 15% but a preferred range of concentrations is 0.2% to 1%.

For gelling to occur, particularly of gellan gum, monovalent or divalent cations must be present in the composition.

Suitable cations include sodium, potassium, magnesium and calcium. The ionic concentration is chosen according to the degree of gelling required, and allowing for the effect that the ionised drug present may have on gelling. At a 0.2% gum concentration, the divalent ions, calcium and magnesium give maximum gel hardness and modulus at molar concentrations approximately one fortieth (1/40) of those required with the monovalent ions,

sodium and potassium. A finite concentration of each cation is required to induce gelation. For the nasal formulation of the invention the ionic strength is kept sufficiently low to obtain a low viscosity formulation but sufficiently high to ensure gelation once administration into the nasal cavity where gelation will take place due to the presence of cations in the nasal liquid. The ionic strength for a 0.5% gellan gum can be in the range of 0.1 mM - 50mM for monovalent cations with the preferred range being 1mM - 5mM and 0.1mM - 5mM for divalent cations with the preferred range being 0.15mM - 1mM. For higher concentrations of gellan gum the ionic strength should be lowered accordingly.

The liquid formulations are administered using well-known nasal spray devices. If the formulations are freeze-dried, they can be administered using a nasal insufflator, as for the microsphere preparations.

In a liquid formulation, the polymeric material will typically be provided in a concentration of from 0.01% to 20%, preferably 0.05-10%, more preferably 0.1% - 5%. The compositions of the invention can also contain any other pharmacologically acceptable, non-toxic ingredients such as preservatives, antioxidants, flavourings, etc. Benzalkonium chloride may be used as a preservative.

Example 1

Into a 20 ml volumetric flask was weighed 100 mg of chitosan glutamate (Sea Cure +210). 5 ml of water was added to the chitosan which was left to stir overnight.

Into a beaker was weighed 1.36 g of potassium dihydrogen phosphate and 2.80 g of sodium chloride. The salts were dissolved in 80 ml of water, the solution adjusted to pH 5.7 using 2N NaOH solution and then made to 100 ml with water.

When the chitosan had dissolved, 5 ml of the phosphate buffer solution was added.

A formulation containing 10 mg/ml ICAM and 5 mg/ml chitosan was prepared by diluting the solution of chitosan in phosphate butter 1:1 with 20 mg/ml ICAM solution.

Example 2

Into a 3 ml glass vial was weighed 10 mg of gellan gum (Kelcogel, Kelco Inc.) To the glass vial was added 1.8 ml of 11 mg/ml ICAM solution, 0.05 ml of 4 mg/ml benzalkonium chloride solution and 0.15 ml of water.

A small magnetic stirrer bar was added to the vial, and the contents stirred at room temperature for 24 hours to disperse the gellan gum.

Example 3

Into a 250 ml conical flask were weighed 500 mg of "Eldexomer" starch microspheres obtained from Perstorp, Sweden.

To the conical flask containing the microspheres was added 31 ml of water and 1.6 ml of 12.5 mg/ml ICAM solution.

The flask contents were gently mixed and then left to stand for 30 minutes.

The contents of the conical flask were frozen by immersing the flask into liquid nitrogen. The flask was swirled during freezing to obtain a homogeneous mixture.

The flask was transferred to a freeze drier and the contents lyophilised for 24 hours. The resulting product was a free flowing powder containing 1 mg of ICAM/21 mg of formulation.

Example 4

Into a 10 ml volumetric flask was weighed 1.0 g of gelatin which was dissolved in 5 ml of water by warming to 35-40 °C.

To the gelatin solution was added 1.8 ml of 22 mg/ml ICAM solution. The flask contents were made to volume with water.
Into a beaker was measured 90 ml of 1% w/v Span 80 in soya oil. The beaker contents were warmed to 35-40°C on a hot-plate.

The warmed Span/soya oil mixture was removed from the hot-plate and was stirred at 1000 rpm using an overhead stirrer.

The 10 ml of ICAM/gelatin mixture was added to the stirring oil and stirred at 1000 rpm for 2 minutes.

While stirring continued, the beaker containing the emulsion was cooled to 15°C by surrounding in ice. Dropwise, 100 ml of acetone was added to the cooled, stirring emulsion.

The gelatin/ICAM microspheres were recovered by centrifugation, washed with acetone and left to dry at room temperature.

The result was a free-flowing powder containing 1 mg of ICAM/26 mg of formulation. The mean diameter of the microspheres was measured, using laser diffraction, to be 50 μm.

Example 5

300 mg of gellan gum was dissolved in 35 ml of water and 15 ml of 20 mM NaCl and heated to 60°C while stirring. The gellan gum solution was then cooled to 40°C. 500 mg Pirovadir was dissolved in 50 ml ethanol and sonicated. The drug solution was added to the gellan gum solution during stirring and heating to 70°C for 40-60 mins. to evaporate the ethanol. The volume was made up with water to 100 ml.

Example 6

100 mg cyclodextrin was dissolved in 5 ml of water during sonication and 100 mg Pirovadir added together with 300 μl 1M HCl. The formulation was sonicated for 10 mins and the pH adjusted to 4.0 by addition of 0.1 m NaOH and the volume adjusted to 10 ml.

2 g of Amylodextrin was added to 10 ml water and heated to 90°C before cooling. The drug solution was added to the amylodextrin gel and stirred. 100 ml of soya oil was added to the gel and the formulation was homogenised at 6500 rpm for 3 min. The emulsion was added to 500 ml soya oil and stirred at 1500 rpm, heated to 100°C and cooled. The microspheres were collected on a 0.5 μm filter and washed. The microspheres obtained were 10 - 150 μm in diameter.

Example 7

100 mg Pirovadir was dissolved in 20 ml of ethanol, sonicated and added to 1.9 g of starch microspheres in 30 ml of water under stirring. The suspension was heated to 70°C for 40-60 mins. to evaporate the ethanol and freeze dried on an Edwards Modulyo freeze dryer.

Example 8

7.5 g hydropropyl β-cyclodextrin was dissolved in 30 ml water and 500 mg Pirovadir was added together with 1.5 ml of 1 M HCl and sonicated. The pH was adjusted to 4.0. 300 mg gellan gum was dissolved in 50 ml water (containing 15 ml 20 mM NaCl) heated to 60°C

and equilibriated for 10 mins. The drug solution was heated to 60°C and slowly poured into the gellan gum solution during stirring. The volume was made up to 100 ml.

Example 9

500 mg of medium viscosity chitosan glutamate was dissolved in 50 ml of water. 26 mg of ICAM was dissolved in the chitosan solution. The chitosan/ICAM solution was spray-dried using a Lab-Plant SD-04 spray-dryer (Lab-Plant, Huddersfield, UK). The drying temperature was set at 100°C. Microspheres of approximately 5 μm diameter were formed.

Example 10

1000 mg of gelatin was dissolved in 50 ml of water at 40°C. 52 mg of ICAM was dissolved in the gelatin solution. The chitosan/ICAM solution was spray-dried using a Lab-Plant SD-04 spray-dryer (Lab-Plant, Huddersfield, UK). The drying temperature was set at 100°C. Microspheres of approximate 5 μm size were formed.

Example 11

An aqueous solution was prepared containing 2.1 mg/ml ICAM, 1.4 mg/ml Mannitol and 0.7 mg/ml PBS. The solution was spray-dried at 100°C to form microparticles of approximately 5μm size. 10 mg of spray dried ICAM and 100 mg of Eldexomer starch microspheres were weighed into a bottle and placed on to a roller mixer for 30 minutes. The resulting formulation consisted of starch microspheres coated with particles of spray-dried ICAM.

Claims

1. A nasal delivery composition for the administration of an antiviral agent based upon a bioadhesive formulation.

2. A composition as in claim 1 based on a microsphere system.

3. A composition as in claim 1 based on gellan or alginate.

4. A composition as in claim 1 based on Chitosan.

5. A composition as in claim 1 where the drug is Pirovadir

6. A composition as in claim 1 where the drug is α-interferon

7. A composition as in claim 1 where the drug is ICAM-1

8. A composition as in claim 1 where the drug is a sialidase inhibitor.

9. A composition as in claim 2 where the microspheres are made from starch, amylodextrin, amylopectin and crosslinked variants thereof.

10. A composition as in claim 2 where the microspheres are made from gelatin.

11. A composition as in claim 2 where the microspheres are made from alginate.

12. A composition as in claim 2 where the microspheres are made from Chitosan.

13. A composition as in claim 2 where the microspheres are between 10 and 100 microns in size.

14. A composition as in claim 1 where the bioadhesive material is Chitosan.

15. A composition as in claim 1 where the bioadhesive material is Welan, Xanthan or Rhamsan.

16. A method for the nasal administration of an antiviral agent based upon a bioadhesive formulation.